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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,321	07/13/2001	Yousuke Takahama	31671-173265	2334

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,321	TAKAHAMA, YOUSUKE	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *13-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response filed on 8/19/04 have been entered. Claims 1-19 are pending in the instant application. This application contains claims 13-19 drawn to an invention non-elected without traverse in the response received on 11/03/03. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 1-12 are currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Information Disclosure Statements

The IDS filed on 8/19/04 has been considered. A copy of the signed IDS is attached to this office action.

Claim Rejections - 35 USC § 112

The rejection of claims 1-12 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of applicant's amendments to the claims.

Applicant's amendments have necessitated the following new grounds of rejection.

Claim 3 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim as amended recites, " .. wherein the foreign DNA comprises at least a gene coding a substance...". It is unclear what is meant the word "coding". In this context, the correct term is "encoding". Amendment of the claim to recite "encoding" would overcome this rejection.

Claim 9 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim as amended depends on claim 8 and recites, "The method of sustaining a gene therapeutic effect and avoiding immune response caused by a foreign DNA and/or its expression product in gene therapy according to claim 8, ..". There is no antecedent basis for the phrase , "and avoiding immune response caused by a foreign DNA and/or its expression product in gene therapy" in claim 8. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 3-8, and 10-12 under 35 U.S.C. 102(b) as being anticipated by DeMatteo et al. (1997) J. Virol., Vol. 71 (7), 5330-5335, is withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 103

The rejection of claims 1-12 under 35 U.S.C. 103(a) as being unpatentable over Ilan et al. (1996) J. Clin. Invest., Vol. 98 (11), 2640-2647, in view of DeMatteo et al. (1997) J. Virol., Vol. 71 (7), 5330-5335, and further in view of Bakker et al. (1999) J. Immunol., Vol. 162, 3456-3462, is maintained. Applicant's amendments to the claims and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant's claims as amended recite methods of acquiring immunological tolerance to a foreign DNA or methods of sustaining a gene therapeutic effect comprising providing an immature T lymphocyte transfected with the foreign DNA and introducing the immature T lymphocytes into thymus. The applicant further claims said methods wherein the foreign DNA comprises an adenoviral vector, or wherein the foreign DNA comprises a gene which causes allergy or autoimmunity, or which is a peptide therapeutic medicament.

The applicant argues that Ilan et al. does not desribe or suggest that imunological tolerance occurs by transferring a foreign DNA into immature T lymphocytes and introducing these cells into thymus. The applicant further argues that the skilled artisan would not be motivated to follow the method of Ilan because Ilan describes the direct administration of adenovirus to the thymus which could lead to systemic toxicity. In response, the office disagrees with the applicant's interpretation of the teachings of Ilan et

al. First, Ilan et al. clearly teaches that introduction of foreign antigen into the thymus results in the induction of immunological tolerance to the foreign antigen. Further, Ilan et al. teaches two different methods to introduce the foreign antigen to the thymus. While Ilan et al. does teach the direct administration of recombinant adenovirus, Ilan et al. also clearly teaches the administration of **cells** transduced with the recombinant adenovirus (Ilan et al., page 2640). Specifically, the previous office action stated that Ilan et al. teaches that in mammals pretreated by thymic injection of cells infected with recombinant adenovirus encoding a therapeutic gene such as human BUGT1, a second intrahepatic injection of the recombinant adenovirus resulted in sustained gene expression of at least 7 weeks (Ilan et al., page 2640). Ilan et al. further teaches that protein other than BUGT1 can be used to generate central tolerance, such as proteins associated with autoimmune disease or allograft rejection (Ilan et al., page 2641, column 1). As applicant's claims as amended now read on the introduction of transfected cells to the thymus, the teachings in Ilan et al. for administering cells transfected with an adenovirus encoding a therapeutic protein to the thymus in order to induce tolerance to the protein are the teachings relevant to the instant rejection, not the teachings for direct injection of adenovirus. Further, since Ilan et al. does in fact teach the adminsitration of recombinant cells, applicant's concerns about the direct administration of adenovirus are misplaced.

The applicant further argues that DeMatteo et al. also teaches the direct administration of adenovirus and presents evidence in the form of post-filing references that systemic administration of adenovirus can cause toxicity. However, Ilan et al. has already been cited as the primary reference teaching the administration of cells transfected with adenovirus to thymus. Thus, as noted above, concerns of systemic

toxicity are not relevant. Further, DeMatteo et al. was cited to supplement the teaching of Ilan et al., by teaching that adenovirus is capable of infecting fetal T lymphocytes in fetal thymus and further that the transduced fetal T lymphocytes induce tolerance (DeMatteo et al., page 5330, abstract, and Figure 1). It is also noted that DeMatteo et al. teaches that by using a cellular carrier to prevent viral extravasation into the periphery, adverse systemic reactions to adenovirus can be avoided (DeMatteo et al., page 5334, column 2).

Regarding the teachings of Bakker et al., the applicant argues that Bakker et al. does not teach that fetal thymocytes infected with adenovirus can induce tolerance. In response, Bakker et al. was cited to further supplements Ilan et al. and DeMatteo et al. by teaching methods of infecting fetal T lymphocytes with recombinant adenovirus *in vitro* in fetal thymic organ culture (Bakker et al., page 3457). Bakker et al. further teaches that fetal thymocytes infected with adenovirus develop into single positive mature T lymphocytes which ultimately migrate to the periphery (Bakker et al., page 3458, Figure 1, and page 3456). The requisite teachings of the induction of tolerance are provided by Ilan et al., and supplemented by DeMatteo et al.

Furthermore, the previous office action sets forth clear reasons why the combination of Ilan et al., DeMatteo et al., and Bakker et al. renders the instant invention obvious. The previous office action stated that motivation to substitute fetal T lymphocytes for hepatocytes in the methods of Ilan et al. is provided by both Ilan et al. and DeMatteo et al. In the methods of tolerance induction taught by Ilan et al., suppression of mature T cells by antilymphocyte serum was used to prevent reactivity of mature T cells with the adenoviral proteins (Ilan et al., page 2640). DeMatteo et al. also teaches that in adult mice, as opposed to neonatal mice, induction of tolerance by

intrathymic administration of adenovirus requires suppression of mature T cells and is further aided by using a cellular carrier to prevent viral extravasation into the periphery (DeMatteo et al., page 5334, column 2). In view of the need to suppress mature T cells in order to effectively achieve central tolerance by administering adenoviral infected cells to the thymus, the skilled artisan would have been motivated to re-introduce fetal T lymphocytes into the thymus in order to stimulate repopulation of the periphery with mature T lymphocytes. Thus, based on the motivation to introduce fetal T lymphocytes to repopulate mature T lymphocytes in hosts treated with antilymphocyte serum, it would have been *prima facie* obvious to the skilled artisan to substitute fetal T lymphocytes for the hepatocytes in the methods of inducing central tolerance to recombinant adenoviruses taught by Ilan et al. Further, based on the successful infection of fetal T lymphocytes taught by Bakker et al., the skilled artisan would have had a reasonable expectation of success in infecting fetal T lymphocytes with the recombinant therapeutic adenoviruses taught by Ilan et al. and using those infected fetal T lymphocytes to induce central tolerance in adult hosts following intrathymic injection.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER